DOI:
10.1080/17476348.2017.1358619

Document Version
Peer reviewed version

Electrical Stimulation for the Treatment of Obstructive Sleep Apnoea: Review of the Evidence

Abstract

Introduction: Obstructive sleep apnoea is an increasingly prevalent clinical condition with significant impact on individuals and public health. Continuous positive airway pressure therapy is the standard treatment, but adherence is limited and alternative treatments are needed. In this context, non-invasive and invasive methods for electrical stimulation of upper airway dilator muscles have been demonstrated to be effective in selected patients.

Areas covered: Investigations on the clinical effects, safety, and tolerability of non-invasive and invasive electrical stimulation of the upper airway for the management of obstructive sleep apnoea. Following a search of the relevant literature published on Pub Med this review is focused mainly on data obtained from randomized clinical trials and clinical studies.

Expert commentary: The available evidence provides a rationale to consider upper airway electrical stimulation as treatment for selected patients with obstructive sleep apnoea, who have poor adherence or experience difficulties with continuous positive airway pressure therapy. Non-invasive stimulation using transcutaneous electrodes and implantable hypoglossal nerve stimulator technologies may provide an alternative to continuous positive airway pressure for the treatment of obstructive sleep apnoea via restoration of neuromuscular tone and improved upper airway patency.

Key words: obstructive sleep apnoea; upper airway patency; genioglossus muscle; hypoglossal nerve stimulation; transcutaneous electrical stimulation; implantable stimulation technologies.

1. Introduction

1.1 Obstructive Sleep Apnoea as a worldwide health challenge

Obstructive sleep apnoea (OSA) is a serious, potentially life-threatening condition caused by recurrent episodes of total and/or partial upper airway (UA) collapse occurring during sleep, accompanied by oxyhaemoglobin desaturation, large intra-thoracic pressure changes and arousal from sleep and, in severe cases, hypercapnia [1]. OSA is the most common respiratory sleep disorder and its prevalence is increasing due to the obesity epidemic and aging population [2, 3]. It has been estimated that symptomatic OSA affects up to 10% of middle-aged men and 3% of middle-aged women [3, 4], and it is associated with multiple comorbidities, including arterial hypertension [1], arrhythmias [5], coronary artery disease [6], right heart failure [7], stroke [8], and metabolic diseases (i.e. metabolic syndrome, impaired glucose tolerance, and diabetes mellitus) [1, 9], which concur to worsen prognosis. Untreated OSA has been linked to neurocognitive impairment and motor vehicle accidents [10, 11].

Currently, continuous positive airway pressure (CPAP) represents the first line therapy, recommended by guidelines for treatment of patients with moderate-to-severe OSA [12, 13]. CPAP aims to maintain upper airway patency by providing an air splint [14]. It reduces snoring, the apnoea/hypopnea index (AHI), and daytime sleepiness; furthermore, it improves neurocognitive function, driving risk, and sleep-related quality of life [15, 16]. CPAP may also reduce long-term cardiovascular risk in patients with OSA [17]. However, recently McEvoy *et al*. in the Sleep Apnea cardioVascular Endpoints (SAVE) trial [18] reported that adding CPAP to usual care, despite being associated with a reduction in

symptoms of daytime sleepiness and improving health-related quality of life, mood, and work attendance, did not reduce the risk of serious cardiovascular events compared to usual care alone. This outcome could be explained by the limited adherence to CPAP treatment. In clinical services, low adherence to treatment occurs in up to 40-50% of the patients with OSA; in the SAVE trial the mean CPAP usage at 1, 6, and 12 months was 4.4 ± 2.0, 3.8 ± 2.3, and 3.3 ± 2.4 h/night, respectively. Considering that approximately only half of the OSA patients continue to use prescribed CPAP reliably long-term [12, 19] it is likely that a large portion of sleep apnoea patients are inadequately treated. In such cases therapeutic alternatives to CPAP are required [12]. These include "sleep hygiene" (i.e. avoiding alcohol and sedatives), weight loss, mandibular advancement devices [20], positional therapy, and upper airway (UA) surgery [12]. However, these alternative measures are usually not comprehensive and definitive solutions, as they have been demonstrated to be effective in specific and selected cases; it has also to be considered that UA surgery has operative risks and potential associated morbidity.

Responding to the high prevalence of untreated OSA and its impact on worldwide healthcare resources, a new type of treatment has been refined in recent years. This involves use of electrical stimulation of the upper airway dilator muscles (Figure 1).

In this review, the aim is to describe the evidence related to electrical stimulation of the UA dilator muscles in OSA in clinical practice.

1.2 Neuromuscular tone of the upper airway and the pathophysiology of Obstructive Sleep Apnoea

Several decades ago, Remmers *et al*. reported a direct relationship between loss of genioglossus muscle activation during sleep and UA collapsibility in patients with OSA [21]; this seminal observation led to the hypothesis that OSA could be treated by electrical stimulation of the parapharyngeal muscles with transcutaneous, intraoral, or intramuscular electrodes [22, 23].

The anatomy of the upper airway is complex, as is the function, required for swallowing, respiration, and vocalization, which is related to the tightly controlled and complex motor tasks required for speech. In human beings, UA obstruction during sleep is more prevalent than in other primates because the hyoid bone, a key anchor for pharyngeal dilator muscles, is not rigidly attached to skeletal structures. The human pharynx has no rigid support except at its cranial and caudal ends, where it is anchored to bone (in its upper side) and cartilage (larynx) caudally. Therefore, pharyngeal cross-sectional area will vary with intra-luminal pressure [24, 25]. Studies using nasal pharyngoscopy, computer tomography (CT) and magnetic resonance imaging, or pharyngeal pressure monitoring, have shown that closure occurs in most subjects with OSA at one or more sites within the oral pharyngeal region, and that this region may be narrower in OSA patients compared to controls during wakefulness [26 – 29]. Although the retropalatal region of the oropharynx is the most common site of airway collapse, narrowing is a dynamic process, varying markedly among and within subjects and often including the retroglossal and hypopharyngeal areas [30, 31]. Neuromuscular control of breathing during sleep also plays a key role in OSA pathogenesis, e.g. central respiratory output, tonic activity of pharyngeal dilator muscles activity, arousal threshold and loop gain. The concept of 'loop

gain' is an engineering term, which defines the 'gain' of the negative feedback loop that regulates ventilation in response to a ventilatory disturbance [32]; if the magnitude of the increase in ventilation is greater than or equal to the magnitude of the preceding apnoea or hypopnea, i.e. a high loop gain, then the system is highly unstable and will fluctuate between hypo- and hyperventilation [33]. There are two types of control system gain, the controller gain (the control of variables relating to hypercapnic and hypoxic ventilatory responses) and the plant gain (the ability to eliminate CO_2 and the size of oxygen stores), and they are major determinants of loop and ventilatory stability [34]. Sleep reduces controller gain relative to wakefulness, and, more importantly, upper airway tone, particularly in rapid eye movement (REM) sleep. A high loop gain promotes recurrent apnoea as a response to an initial disturbance, such as a sigh, because it is overcompensated, while a low loop gain inhibits subsequent variability in the breathing pattern [35]. Many patients with severe OSA have a high loop gain, as determined by the propensity for periodic breathing observed during ventilatory assist [36] or a greater ventilatory response to carbon dioxide (CO_2) [34, 37].

Multiple parapharyngeal dilator muscles work together to counteract the dual forces of negative intraluminal pressure from diaphragmatic excursion and positive extraluminal tissue pressure [25]. The genioglossus is the largest and strongest UA dilator. The activation of noradrenergic neuron can selectively stimulate the genioglossus muscle, but the mono-aminergic neuron activity may decrease the dilating force of the UA when the noradrenergic neuron is inhibited during sleep [38]. Activation of the genioglossus muscle alone can reduce collapsibility but it may not always prevent significant obstruction [39];

In individuals with a collapsible UA, dilating forces are represented by several other groups of motoneurons and the muscles they innervate, including motor trigeminal (V), facial (VII), glossopharyngeal (IX), motor vagal (X), and hypoglossal (XII) nerves. Muscles regulating lung volume, neck and jaw position also contribute to UA patency, and thus motoneurons located in the cervical ventral horn impact on UA patency [25].

In patients with OSA, the presence of cranial anatomic dysmorphisms, reduced tone of parapharyngeal dilator muscles (secondary to aging, alcohol assumption [40 – 41], smoking [42, 43], increased systemic inflammation [44]), and the higher positive extraluminal tissue pressure due to fat deposition on the neck, are important contributory factors that determine the onset of recurrent episodes of apnoea and/or hypopnoea during sleep. The SPAtial Modulation of Magnetization (SPAMM) technique allows quantification of respiratory-related movement of the UA soft tissue displacement; using this method, it has been demonstrated that a high AHI (> 50 events/hour) is associated with minimal movement of the posterior tongue and the lateral walls of the nasopharynx during wakefulness [45].

Starting from this known pathophysiology, several techniques to stimulate the muscles of the upper airway with electric current to increase neuromuscular tone and maintain UA patency during sleep have been developed.

2. Electrical stimulation of the upper airway and its role in clinical practice for the treatment of Obstructive Sleep Apnoea

In recent years, several methods to stimulate parapharyngeal muscles have been developed [46] and refined as discussed in the next sections.

2.1 Non-invasive methods for upper airway stimulation

In 1989 Miki *et al*. described the effect of genioglossus electrical stimulation in anesthetised dogs [47]; they observed improved UA patency with graded increases in stimulation frequencies in awake, spontaneous breathing animals. They also conducted the first experiment in humans to verify the tolerability and efficacy of UA stimulation [48]: six OSA patients underwent percutaneous electrical stimulation of the genioglossus during sleep. Compared to control nights, the authors demonstrated that submental stimulation significantly improved AHI, longest apnoea duration, and number of times per hour that oxygen saturation dropped below 85%, thus proving the concept that this stimulation can reduce the incidence of apnoea episodes and promote deeper sleep. No adverse side effects were reported. An apnoea demand-type of stimulator, hence, may be an effective non-invasive treatment for OSA. These early favourable results [48], however, could not be reproduced by subsequent studies in other centres performed with either external or percutaneous electrical stimulation of UA. Successful stimulation of UA muscles and relief of UA obstruction without causing arousal from sleep could not be achieved with submental or intraoral stimulation [49], neither using submental electrodes or fine wire electrodes placed into the neurovascular bundle [50], nor with transcutaneous electrical stimulation applied in the submental or infrahyoid regions [51]. In particular, contrary to the first results [49], in 1992 Edmonds *et al*. showed that, despite similar electrode

placement and stimulation parameters, transcutaneous electrical stimulation applied in the submental and subhyoid regions in eight adults affected by OSA failed both to prevent the onset of UA collapse and the re-establishment of UA patency when stimulation was begun after apnoea onset during sleep. Moreover, when applied during wakefulness, transcutaneous stimulation did not provide UA enlargement as evaluated by CT [51]. According to Decker *et al*. [50] the application of surface stimulation had inconsistent effects during apnoeic events, leading to termination of the apnoeas only in 22% of the cases; fine-wire functional electrical stimulation also had a limited impact, terminating 23% of the apnoeic events. They concluded that during sleep subjects tolerate both surface and fine-wire functional electrical stimulation at higher stimulus intensity than during wakefulness. However, both approaches were judged to have an inconsistent effect on apnoeas during sleep [50]. In 1994, Hida *et al*. reported the effect of submental stimulation applied during five consecutive nights in eight OSA patients, and during two consecutive nights in five controls. They found a positive effect of electrical stimulation in terms of improvement in AHI (53.8 ± 7.0 *vs* 27.3 ± 5.7 events per hour, $p<0.01$), total apnoea duration (41.1 ± 6.1 *vs* 17.6 ± 3.9% of total sleep time, $p<0.01$), mean duration of apnoea (27.4 ± 3.2 *vs* 23.0 ± 2.1 seconds, $p<0.05$), and oxygen saturation (SaO2) < 85% events/hour (32.5 ± 7.0 *vs* 11.3 ± 3.3, $p<0.01$): all parameters significantly improved during the fifth night of stimulation [52]. A year later, another study could not confirm the effectiveness of UA electrical stimulation in OSA. Using both submental and intraoral electrodes when awake and during sleep, in seven patients with severe OSA (mean respiratory disturbance index, RDI, 55 ± 6 per hour of sleep), Guilleminault *et al*. did not find changes in the

number of apnoeas and hypopnoeas, amount of oxygen desaturation, and mean duration of respiratory events, compared to baseline measurements [49]. Although they concluded that intraoral stimulation could act on dilator muscles, the complex muscle structure within the tongue may have multiple roles and could modify the UA shape without opening the UA. In order to elucidate whether the co-activation of both the tongue protrudor and retractor muscles decrease the compliance of the retroglossal airway wall, Isono *et al*. [53] performed electrical stimulation of the tongue by two intraoral electrodes bilaterally in seven male OSA patients. Measuring pharyngeal cross-sectional area, the authors found that this procedure did not further dilate the oropharyngeal area with higher pressures, although the oropharyngeal area increased during stimulation with lower pressures (0.8 ± 9.0 *vs* 1.7 ± 1.8 cm^2, $p<0.05$) [53]. Based on these results, in 2001 Oliven *et al*. [54] undertook a study in which seven healthy volunteers and six OSA patients underwent electrical stimulation of the sublingual surface; the results showed that stimulation of the tongue improved airflow during sleep it was unsuccessful in reopening the UA in the presence of complete apnoea [54]. This study did not assess the tolerability or the potential clinical efficacy of UA electrical stimulation and was designed to verify the site within the UA that could respond best to stimulation. More recent studies have been designed to assess the potential clinical role of electrical stimulation of UA, both in terms of efficacy and of patient comfort. In 2008, Hu *et al.* [55] developed a percutaneous 50 Hz biphasic electrical nerve stimulator in which the intensity of stimulation could be regulated automatically to meet the needs for clinical treatment. Biphasic electrical current pulses with equal electrical charge were used to avoid tissue injury during long-

time stimulation. The electric tension was 12-80 V peak-to-peak and the intensity levels of stimulation were individually set up during wakefulness in each subject. Twenty-two OSA patients (six with severe OSA) were studied: the results showed that the mean of RDI, oxygen desaturation index (ODI), and longest apnoea significantly decreased (30.9 to 12.5 events per hour, 33.0 to 18.6 events per hour, and 57.6 to 29.5 seconds, $p<0.01$ respectively) [55]. In 2011, Steier *et al.* reported similar results in terms of improved ODI and AHI, and improvement in oxygen saturation [22]: using continuous transcutaneous submental 30-Hz electrical stimulation - the mean current was 10.1 (3.7) mA - in eleven patients with known OSA during one monitored night of sleep they confirmed that stimulation of the genioglossus muscle caused a measurable and reproducible contraction of the tongue and pharyngeal structures, reducing the RDI (28.1 to 10.2 events per hour, $p = 0.002$), ventilatory load and neural drive [22].

Although the promising results from these studies support the potential role of transcutaneous electrical stimulation as a treatment in OSA, the previous studies had important limitations, particularly the absence of well-matched control groups. To address this limitation, a randomised sham-controlled trial of transcutaneous electrical stimulation in OSA (TESLA trial) has been conducted and recently published [56]. The study was of 36 patients affected by moderate-to-severe or symptomatic mild obstructive apnoea, with an AHI median of 28.1 (interquartile range, IQR 19.0–57.0) and ODI median of 25.7 (IQR 16.0–49.1) events per hour, who were randomly assigned to one night of sham and one night of electrical stimulation delivered by surface electrodes attached bilaterally midway between the chin and the angle of the mandible in the submental area

(stimulation patches of 4 x 4 cm). Between stimulation and sham nights there was a wash-out period of at least three nights. During active treatment (current of 626.1 μA (409.8 mA)), the primary outcome of the trial, the ODI, improved modestly, by a mean of 4.1 events per hour (95% confidence interval, CI −0.6 to 8.9, p=0.026) for the whole group, when compared with sham stimulation; no differences were observed in the oxygenation levels and there were no significant improvements in the AHI. Although the total AHI did not change during stimulation, there was a shift in the ratio from obstructive apnoeas to hypopnoeas when electrical current was applied, indicating an incomplete resolution of the UA obstruction during apnoeas (Figure 2). However, 47.2% of the patients were identified as responders in that they experienced an improvement in the AHI by > 50% or in the ODI >25% or to an AHI or ODI <5 events per hour. In this subgroup, the ODI was reduced by 10.0 (95%CI 3.9 - 16.0) events/hour and the AHI by 9.1 (95%CI 2.0 – 16.2) events/hour). The patients' device acceptance was good with patients reporting no skin discomfort or unpleasant sensations at night; there was no difference in subjects' perceived sleep quality between the sham stimulation and the active treatment. Moreover, the patients reported an improvement of their dry mouth after active treatment. This randomised controlled study also demonstrated that transcutaneous electrical stimulation of the UA dilator muscles in OSA can be safely delivered throughout the whole night and is useful to reduce the RDI, even though only modestly, in unselected OSA patients [56].

In 2016, Chwieśko-Minarowska *et al*. [57] published a prospective study and its objective was to compare the effects of daytime transcutaneous electrical stimulation of the genioglossus muscle and CPAP therapy on the quality of sleep, in patients with OSA.

They found that electrical stimulation resulted in a decrease in Pittsburgh Sleep Quality Index (PSQI) values (p=0.012), but did not cause significant changes in ESS and AHI scores (p>0.05), in turn, a decrease in ESS and AHI (p>0.001), but not PSQI values (p = 0.089), was observed after CPAP therapy. Finally, Campbell *et al*. [58] surveyed 162 patients with OSA and the most preferred therapeutic modality was transcutaneous electrical stimulation of the genioglossus muscle (56.7%), followed by hypoglossal nerve stimulation (HNS) (21.7%), CPAP (17.8 %) and mandibular advancement device (3.8%).

Well-designed future studies should focus on prospective identification of responders. It is likely that this method is more effective in OSA patients with an anterior pharyngeal wall collapse, and less efficacious in patients with excessive adipose tissue, large tonsils, and adenoids, or other anatomic abnormalities. This may explain the failure to respond to this method in some patients [50]. In addition, there are no data on the long-term acceptability and compliance yet.

In summary, well-designed studies, including larger groups of patients, are needed to determine the efficacy of this type of treatment, its safety and tolerability, and the optimal duration of electrical stimulation and to identify the individuals with OSA who may benefit.

2.2 Invasive methods for electrical stimulation of the upper airway

Following the promising results derived from implantable nerve stimulation technology in other medical conditions (e.g. sacral nerve stimulation for incontinence [59], vagal nerve stimulation for seizures [60], spinal cord stimulation for pain [61], and deep brain

stimulation for tremor [62]) [63], Schwartz *et al*. [64] tried to selectively stimulate the hyoglossus and styloglossus muscles (that retract the tongue), and the genioglossus (that protrudes the tongue) during sleep using fine-wire electrodes placed intramuscularly via an oral approach. They reported a significant improvement in maximal inspiratory airflow during protrusor stimulation, with no arousal from sleep; however, no attempts were made to measure UA collapsibility.

Oliven *et al*. [65] demonstrated that, in 8 anesthetised dogs, selective intramuscular stimulation of the hypoglossus significantly lowered the UA collapsibility, defined and measured as the "critical" occlusion pressure (P_{crit}). The same group studied the response to electrical stimulation in the UA pressure-flow relationship during sleep with an implanted hypoglossal nerve stimulator in five patients; fine-wire electrodes were inserted into the genioglossus. The results confirmed that P_{crit} decreased similarly during both hypoglossus and genioglossus electrical stimulation (ΔP_{crit} was 3.98 ± 2.31 and 3.18 ± 1.70 cmH_2O, respectively) [66].

However, only in 2001 was the first pilot study in human beings published that studied the effect of implantable HNS on OSA [67]. After the development of new implantable hypoglossal nerve-stimulating devices, Schwartz *et al*. [67] conducted a clinical trial to test this device (Inspire I, Inspire Medical Systems™, Maple Grove, MN, USA) in eight apnoeic patients for six months. The system consisted of three components: a tripolar half-cuff nerve stimulation electrode, an implantable pulse generator, and a respiratory pressure sensor placed against the pleura to detect respiratory effort. "End expiration" triggered the implantable pulse generator at the onset of inspiration. Implantation of the HNS required

general anaesthesia. Sleep studies were performed at 1, 3, and 6 months postoperatively and seven of the eight participants had significant reductions in their AHI and in the overall group non-rapid eye movement (REM) sleep AHI improved from 52.0 ± 20.4 to 22.6 ± 12.1 ($p<0.001$) events per hour. All participants tolerated stimulation once parameters were appropriately adjusted. Despite the encouraging results, broken electrodes and sensor malfunction occurred in five of eight participants, thus precluding use beyond the 6-month study period [67].

Addressing the technical limitations of this study, multiple investigators and medical device companies spent years improving the product. In 2011, Eastwood *et al*. [68] reported on the safety and effectiveness of a new generation implantable hypoglossal nerve stimulator therapy system (HGN System, Apnex Medical™ Inc, St Paul, MN, USA) in a phase II trial carried out at four Australian centres. Twenty-one patients with moderate-to-severe OSA who were unable to tolerate CPAP underwent surgical implantation of the dual respiratory sensing leads, which were tunnelled subcutaneously along the costal margin. These sensors functioned as thoracic impedance sensors and were used to determine respiratory effort. Intra-operative fluoroscopy was used to confirm placement of the electrode cuff by demonstrating an expansion of the retroglossal airway with device activation. Sleep studies were performed at 1, 3, and 6 months. Nineteen of the 21 participants in the study had baseline and 6-month polysomnography, and showed a significant improvement from baseline in AHI (43.1 ± 17.5 to 19.5 ± 16.7 events per hour, $p<0.05$) and Epworth Sleepiness Scale (ESS) score (12.1 ± 4.7 to 8.1 ± 4.4, $p<0.05$). Only two adverse events were reported: an infection requiring device removal

and stimulation lead cuff dislodgement requiring replacement [68]. Testing the same device, Goding *et al*. [69] enrolled 26 OSA patients with the aim of characterizing the changes in the antero-posterior dimensions of both the retro palatal and retro lingual airway space of the pharynx and hyoid bone position during HNS (Apnex Medical™ Hypoglossal Nerve Stimulation system). All participants were examined by cinefluoroscopy videos under general anaesthesia before and during bursts of electrical stimulation; an increase in retro lingual airway space (9 ± 3 mm) was observed and the anterior displacement of the base of the tongue with stimulation occurred at an average stimulation level of 1.2 ± 0.3 mA. An enlargement of the retro palatal airway was seen in 65% of the cohort; the average increase was 5 ± 3 mm. There was a trend (without significance) towards increased body mass index (BMI) in those participants who failed to show an expansion of the retro palatal airway. Anterior displacement of the hyoid occurred in 92% of participants [69]; the hyoid bone is attached to soft tissue structures related to the pharynx and has been the target for treatment of OSA. Its anterior displacement can be achieved using HNS, which leads to anterior displacement of the base of the tongue and an increase in the anterior-posterior retrolingual airway dimensions of the pharynx [69].

In 2012, another group [70] carried out two consecutive open prospective studies with another device, the Inspire II Upper Airway Stimulation system (Inspire Medical Systems™, Maple Grove, MN, USA), which was in a similar way implanted as the HGN system described above with the exception that this device had only a single sensor for respiration. The study was divided into two parts; in the first, the therapeutic feasibility

and safety of UA stimulation in 22 participants with OSA was assessed and predictive factors for therapeutic success were analysed. After 6 months of follow-up, only six subjects showed a significant and sustained reduction in the AHI compared to baseline; these patients had a BMI > 32 kg/m^2 and an AHI > 50 ($p<0.05$) and were more likely to have complete concentric palatal collapse. In the second part of the study, patients (n = 8) were prospectively selected for a body mass index (BMI) ≤ 32 kg/m^2, an AHI between 20 and 50 events per hour, and a non-complete concentric pattern of palatal collapse during drug-induced sedation endoscopy (DISE); also in these subjects, an improvement in the AHI was found (from 38.9 ± 9.8 to 10.0 ± 11.0 per hour; $p<0.01$) at 6 months post-implant. The ESS and Functional Outcomes of Sleep Questionnaire (FOSQ) improved significantly in the treated patients [70].

The precise placement of the cuff electrode on selected branches of the hypoglossal nerve is essential for the successful delivery of UA electrical stimulation. The optimal site of stimulation ~~a functional breakpoint between retractors and protrusors~~ along the course of the hypoglossal nerve is determined by excluding the most distal branch, which typically innervates the anterior portion of the hyoglossus muscle [71, 72]. With the aim to selectively stimulate the proximal trunk of the hypoglossus nerve, in 2013, another neurostimulation device, ImThera aura6000™ (ImThera Medical Inc., San Diego, CA, USA) system was developed and tested, and the results of the phase I and II trials were reported by Mwenge *et al*. [73]. Currently, there is an ongoing multi-centre phase III trial. The ImThera aura6000™ device is characterised by continuous nerve stimulation without a respiratory sensing lead, but alternates electrical stimulation impulses through different

electrode configurations to rest some neuromuscular groups while others are being stimulated. The electrode cuff is furled around the hypoglossal nerve near the middle tendon of the digastric muscle, so that the six stimulating electrodes are radially in contact with the cylindrical body of the proximal hypoglossal nerve. The initial open-label, single-site, single-arm study was conducted to determine safety and efficacy of ImThera aura6000™ in 13 patients with untreated moderate-to-severe OSA [73]. After 12 months of follow-up the authors describe a significant decrease in the AHI from 45.2 ± 17.8 (baseline) to 21.0 ± 16.5 per hour ($p<0.001$), in the ODI from 29.2 ± 19.6 to 15.3 ± 16.2 per hour ($p=0.001$), and in the arousal index from 36.8 ± 12.5 to 24.9 ± 13.7 events per hour ($p=0.001$). However, there was no improvement in the ESS (from 11 ± 7 to 8 ± 4, $p=0.09$). Tolerability and safety of the hypoglossal neurostimulation was judged to be acceptable, stimulation was neither painful nor did it wake patients who complied with therapy. However, there were two cases of transient ipsilateral hemi-tongue paresis; post-operative swelling lasted for 2 weeks in one patient; three leads broke in two patients; one patient had a Twiddler's syndrome and the implanted pulse generator was manually repositioned, and the stimulation continued without further trouble [73].

In 2014, the largest prospective trial to date was published: the Stimulation Therapy for Apnea Reduction (STAR) trial [74]. 929 patients were enrolled in the study, 724 were screened, and, finally, 126 were eligible and implanted the device. These subjects presented moderate-to-severe OSA (AHI 20–50 events per hour), CPAP intolerance, BMI ≤ 32 kg/m^2, and absence of a complete circumferential pattern of palatal obstruction during DISE. They underwent surgical implantation of the HNS system (Inspire II Medical

Systems™, Maple Grove, MN, USA) and were followed for 12 months to assess effectiveness and adverse events. Devices were titrated in the sleep laboratory during polysomnography to optimize comfort and effectiveness. The primary (AHI, ODI) and secondary outcomes measures (ESS, FOSQ) all demonstrated clinically and statistically significant improvements, in particular the median AHI score at 12 months decreased by -68%, from 29.3 to 9.0 events per hour ($p<0.001$), the ODI score decreased by -70%, from 25.4 to 7.4 events per hour ($p<0.001$). The overall rate of serious adverse events was less than 2%; only two patients had device-related adverse events requiring repositioning and fixation. No permanent hypoglossal nerve weakness, no serious device-related infection requiring removal, and significantly less postoperative discomfort compared to traditional pharyngeal or maxillo-facial sleep apnoea surgeries were reported. A third of the participants reported minor tongue discomfort due to stimulation itself or abrasion of the tongue on an adjacent tooth. Most of these local side effects resolved with adjustment of stimulation parameters or in some cases a dental guard. Adherence was excellent by self-report (86% of participants using the therapy nightly at the 12 months) but detailed objective data monitoring was limited [74]. Successively [75], the first 46 therapy responders from the prospective STAR trial entered a randomized controlled therapy withdrawal phase. The patients were assigned to continue or stop with the treatment (''ON'' or ''OFF'') and, eventually, they were re-assessed. The results indicated that patients in whom the treatment was discontinued still had moderate-severe OSA. The AHI deteriorated with the treatment discontinued (from 7.6 ± 4.0 to 25.8 ± 16.2 events per hour, $p<0.05$). Similarly, self-reported secondary measures (ESS and FOSQ) that had initially

improved deteriorated again when therapy was switched off. Furthermore, in this study, for the first time, the authors highlighted the clinical effect of the HNS on the blood pressure. As mentioned above, OSA is associated with increases in blood pressure through several mechanisms, including activation of the sympathetic nervous system, oxidative stress, and catecholamine metabolism dysregulation [76]. Whereas a lowering effect of CPAP therapy on blood pressure reduction has been demonstrated [77], data on the impact of HNS on blood pressure are limited. Therefore, Woodson *et al*. [75] reported that, even though patients were normotensive, systolic and diastolic blood pressures in the on-going treatment group were significantly lower at 12 and 18 months, whereas blood pressure did not change in the group that discontinued treatment.

A second single-arm, prospective interventional trial was performed using the Apnex™ HGN system device by Kezirian *et al*. [78]. They reported the 12-months outcomes in a group of 31 patients with moderate-to-severe OSA. Primary outcomes included both objective and subjective measurements. Across all subjects, the AHI decreased from 45.4 ± 17.5 to 25.3 ± 20.6 events per hour ($p<0.001$) and the FOSQ score improved from 14.2 ± 2.0 to 17.0 ± 2.4 ($p<0.001$). Interestingly, subjects with a BMI ≤ 35 kg/m^2 (68%, 21/31) demonstrated significantly greater reduction in the AHI and better improvement in symptoms at 12 months compared to the subgroup of patients with a BMI > 35 kg/m^2. Patients demonstrated excellent compliance, using therapy during 86% of nights for an average of 5.4 hours per night. Within the first 6 months, three serious device-related adverse events occurred: an infection requiring device removal and two stimulation lead cuff dislodgements requiring replacement [78].

The analysis of clinical aspects and outcomes of HNS implantation outside the context of a clinical research trial was published by Kent *et al*. [79], presenting results from a retrospective data collection in a single academic sleep centre. The authors showed that HNS therapy, using the Inspire device (Inspire Medical Systems™, Minneapolis, Minnesota) was associated with good adherence (mean 7.0 ± 2.2 h/night), low morbidity, and significantly improved subjective and objective OSA outcome measures. In a group of twenty patients with severe OSA, previously treated with UA surgery, or CPAP, or BiPAP, or oral appliance therapy, the authors found that after a post-operative period of about 3 months, most of the patients presented with a good response to HNS in terms of AHI (reduction of the AHI from 33.3 ± 13.0 to 5.1 ± 4.3; $p<0.001$) and sleepiness (reduction of the ESS from 10.3 ± 5.2 to 6.0 ± 4.4; $p<0.01$). Three patients had HNS related problems, two patients developed a seroma at the incision site in the immediate postoperative period, and one patient experienced prolonged incisional discomfort). These data suggest that HNS treatment can be used in routine clinical practice outside of a clinical trial setting [79]. The importance of evaluating the technical aspects of the surgical procedures was summarised in a recent review by Murphey *et al*. [80], based on the transition of HNS systems from clinical trials to US Food and Drug Administration (FDA)–approved commercial implants. The goal of the review was to describe the learning curve in the surgical procedures using the Inspire device (Inspire Medical Systems™, Maple Grove, MN, USA) to determine the effect of experience on surgical procedure time and complication rates. The authors examined data from 22 study centres and concluded that the implant surgery time decreased significantly with experience (after the first five

implants); however, surgeon experience did not appear to improve outcomes (complication rates and post-operative pain); the safety profile and peri-operative morbidity were acceptable and compared favourably to other implantable device procedures.

Data on the Inspire™ and Apnex™ devices have described the acute response to hypoglossus stimulation [81]. Unilateral stimulation of the hypoglossal nerve during sleep in patients with OSA results in improved inspiratory airflow with increasing stimulation intensity. Airflow returns to baseline before and after the stimulated breath suggesting that hypoglossus nerve stimulation exerts a direct effect on lingual muscles and airway patency without arousing patients from sleep. The stimulation technique of the ImThera aura6000™ device, as mentioned above [71], is continuous; this modality enables a more coordinated activation of the tongue muscles. Rodenstein *et al*. [82], in a brief communication published after the conclusion of 12-month single-site clinical trial [62], speculated that stimulation strengthens the tongue muscles, producing an additive effect that persists after stopping stimulation. However, this is speculation based on findings during the first night off therapy in 10 patients. The tonic-type stimulation might have modified the neural pattern of stimulation of the tongue muscles, either by modifying the agonist–antagonist balance of forces, by modification of the activated motor units, or by impact on the associated cortical areas. At the moment, these hypotheses remain speculative, but underline that neural stimulation can result not only in direct muscle function, but also in altered neuromuscular tone [82].

In summary, HNS for the treatment of OSA is a relatively safe and effective alternative for improving OSA outcomes in individuals with moderate-to-to severe OSA who have failed conventional medical treatment. HNS leads to a clinically significant decrease in observed mean AHI, ODI, and ESS, combined with improvements in several quality-of-life scales. Responders are more likely to be less obese and have less severe OSA, which is also true for the transcutaneous approach. Specific technical features will need to be tested to improve implantable devices effectively and different types of stimulation need to be systematically assessed.

2.3 Hybrid methods

In addition to either the invasive and the non-invasive methods of electrical stimulation new "hybrid" treatments combining the two methods have been proposed. One of these devices is the so-called *Nyxoah system* (Nyxoah S.A. Brussels, Belgium) and consists of a small neurostimulator for the distal branches of the hypoglossal nerve. The device contains two main different parts: the Genio™ Implantable Stimulator (Nyxoah S.A. Brussels, Belgium), an implanted device placed in the submental area adjacent to the genioglossus muscle through surgical procedure, and an external activation chip attached to the skin with a disposable patch, which contains batteries and activates the implantable stimulator through radio frequencies. The technique is minimally invasive when compared to other hypoglossal neurostimulation systems; there is no implanted lead or battery unit, which is claimed to reduce the risk of surgical re-intervention. From a

physiological standpoint it can stimulate the hypoglossal nerve bilaterally. However, there are sparse data on the efficacy of such hybrid methods in patients with OSA. A clinical trial has been concluded (https://clinicaltrials.gov/ct2/show/NCT02312479) and the results are expected to be published.

3. Future developments

Electrical stimulation of the upper airway dilator muscles in OSA can be considered as an evolving non-CPAP therapy. There are new data available from randomised controlled trials for both invasive and non-invasive electrical stimulation [56, 73]. These trials suggest that the treatments are effective in a selected cohort of patients, particularly those who are less obese and who have less severe OSA. Electrical stimulation is well tolerated if stimulation intensity if titrated properly to avoid waking the patients. For invasive stimulation, improving surgical procedures and quality will further reduce complications. Recent studies [74] have shown lower rates of adverse events compared to previous trials [73]. In the STAR trial the overall rate of serious adverse events was less than 2% with two out of 126 participants having a serious device-related adverse event requiring repositioning and fixation of the neurostimulator to resolve discomfort. Despite these promising results in terms of effectiveness, safety, and tolerability of UA electrical stimulation, the costs of devices and surgical procedures make this treatment limit accessibility in publicly funded healthcare systems. A full cost-effectiveness analysis to weigh costs and effectiveness has yet to be performed to demonstrate that UA electrical stimulation is a cost-effective treatment strategy for moderate-to-severe OSA patients

intolerant to CPAP therapy. In a first attempt, Pietzsch *et al*. [83] have shown that UA stimulation on a willingness-to-pay threshold costs $50,000–$100,000/Quality Adjusted Life Year (QALY). However, this study was conducted in the U.S. healthcare system, and the analysis only compared UA stimulation to no treatment. Other healthcare providers may have lower thresholds to define cost-effectiveness.

Non-invasive electrical stimulation in OSA requires further validation of the results of the TESLA trial [56], which showed a rather modest improvement in both ODI and AHI in the whole cohort of patients but significant improvements in responder groups. In particular, better characterisation of responders requires further study, as well as the feasibility of long-term acceptability and outcomes of transcutaneous electrical stimulation in the domiciliary setting.

In summary, there is accumulating evidence that electrical stimulation in OSA is a well-tolerated and effective treatment in responders, which can help to address the problem of the large number of patients that fail, or do not tolerate, CPAP treatment. Electrical stimulation offers another option of non-CPAP therapy in the treatment possibilities for OSA.

4. Expert commentary: 500 -1000 words

Treatment of OSA is recommended for patients symptomatic disease with symptoms of excessive daytime sleepiness and proven cardiovascular risk factors (i.e. arterial or pulmonary hypertension, ischemic heart or cerebral disease, arrhythmia, diabetes mellitus) regardless of severity. The first line therapy, together with measures of sleep hygiene, diet, and physical exercise, is CPAP therapy which is considered the *gold standard*. However, CPAP may not be tolerated and patients long-term compliance tends tends to be low. Although mandibular advancement devices can be used to treat mild OSA, alternative treatment strategies are required. Electrical stimulation of the upper airway has been developed to address this need.

The available evidence on non-invasive and invasive strategies of electrical stimulation of the UA dilator muscles in OSA suggests that this type restores the physiological function of the UA dilator muscles during sleep. Nevertheless, there is a need for further research aimed at comparing these methods with conventional therapies (i.e. CPAP, oral appliances, and other surgical procedures) using a robust methodology to test feasibility and to establish cost-effectiveness. Future studies should concentrate on identifying potential responders to that treatment. Moreover, further studies and clinical trials are needed to evaluate the long-term impact of these methods on blood pressure, metabolic and cardiovascular risk parameters linked to OSA.

Five-year view and future implication

There is mounting evidence that electrical stimulation is a potential treatment for OSA patients who respond to this approach, and that allows clinical translational work to be delivered at the bedside. More data are required to study whether the promising results observed in randomised controlled trials can be replicated in clinical services.

We speculate that in the near future, with the continuous improvement of devices, software and stimulation algorithms and with a better understanding of the phenotype of responders, electrical stimulation for OSA might be used in patients who do not tolerate CPAP, or for those with mild to moderate disease. Future revisions of international guidelines and recommendations for the treatment of OSA need to update the evidence provided by randomised controlled trials and summarised in this review, and this will promote the acceptance of electrical stimulation as alternative treatment to CPAP therapy.

Key issues

- Obstructive sleep apnoea (OSA) is a serious condition affecting sleep quality and causing symptoms like excessive daytime sleepiness, determining most of road traffic accidents.
- Continuous positive airway pressure (CPAP) is the most effective treatment for OSA, however, long-term adherence is limited.
- Alternative treatments like neuromuscular stimulation of the airway dilator muscles have been shown to be effective and are well tolerated.
- The STAR trial confirmed that the stimulation of the muscles through an implantable stimulator of the hypoglossus nerve effectively improves OSA although cost implications have to be considered.
- The TESLA trial has shown that stimulation of the upper airway dilator muscles through transcutaneous electrical current has a modest effect on OSA, but in a subgroup of patients the effect was clinically relevant; this approach was well tolerated but remains to be tested in the community setting.
- Currently, there is a lack of evidence for hybrid devices, and further testing is required.
- Future work could incorporate drug-induced sedation endoscopy to better understand favourable patterns of airway collapse with the aim to identify responders to electrical stimulation.

- Giving the rising evidence of the effectiveness of neuromuscular stimulation of the airway dilator muscles in OSA, future guidelines should consider the aforementioned studies and the recently changed scientific evidence.

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